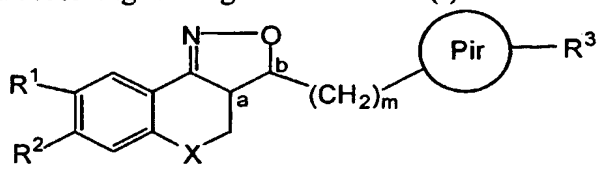
Claims

1. A compound according to the general Formula (I)



(I)

the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the *N*-oxide form thereof, wherein :

X is CH_2, N-R^7, S or O ;

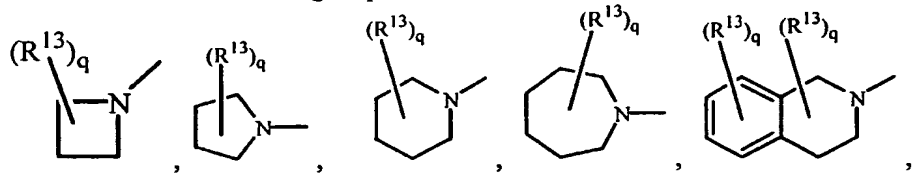
R^7 is selected from the group of hydrogen, alkyl, Ar, Ar-alkyl, alkylcarbonyl, alkyloxycarbonyl and mono- and di(alkyl)aminocarbonyl ;

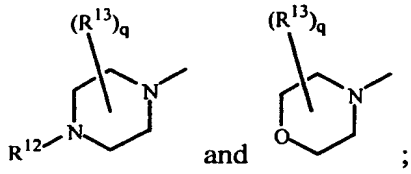
R^1 and R^2 are each selected from the group of hydrogen, hydroxy, cyano, halo, OSO_2H, OSO_2CH_3, N-$R^{10}R^{11}$, alkyloxy, alkyloxyalkyloxy, alkyloxyalkyloxyalkyloxy, tetrahydrofuranyloxy, alkylthio, alkylcarbonyloxy, alkyloxyalkylcarbonyloxy, pyridinylcarbonyloxy, alkylcarbonyloxyalkyloxy, alkyloxycarbonyloxy, alkenyloxy, alkenylcarbonyloxy and mono- or di(alkyl)aminoalkyloxy ;

with the proviso that at least one of R^1 and R^2 is N-$R^{10}R^{11}$ wherein :

R^{10} and R^{11} are each, independently from each other, selected from the group of hydrogen, alkyl, Het, Ar, Ar-alkyl, Het- alkyl, mono- or di(alkyl)aminoalkyl, mono- or di(alkenyl)aminoalkyl, alkylcarbonyl, alkenylcarbonyl, Ar-carbonyl, Het-carbonyl, alkyloxycarbonyl, aminocarbonyl, mono- or di(alkyl)aminocarbonyl, mono- or di(Ar)aminocarbonyl, mono- or di(alkyloxycarbonylalkyl)aminocarbonyl, alkylcarbonyloxyalkyl, alkenylcarbonyloxyalkyl, mono-or di(alkyl)aminocarbonyloxyalkyl, aminoiminomethyl, alkylaminoiminomethyl, N-benzylpiperazinyliminomethyl, alkylsulphonyl and Ar-sulphonyl ; or

R^{10} and R^{11} may be taken together and with the N may form a monovalent radical selected from the group of





wherein :

R^{12} is selected from the group of hydrogen, alkyl, Ar, Ar-alkyl, Ar-alkenyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkylcarbonyl and mono- or di(alkyl)aminocarbonyl ;

each ring having optionally 1, 2 or 3 double bonds and each ring being optionally substituted with q radicals R^{13}, each radical R^{13} independently from each other selected from the group of alkyl, oxo, Ar, Ar-alkyl, Ar-alkenyl and alkyloxycarbonyl and q being an integer ranging from 0 to 6 ;

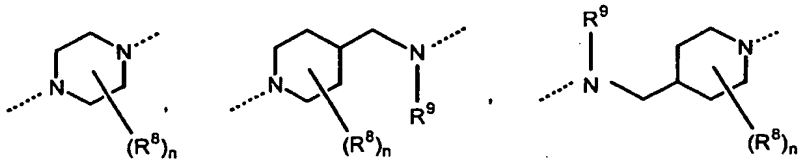
or

R^1 and R^2 may be taken together to form a bivalent radical $-R^1-R^2-$ selected from the group of $-O-CH_2-NR^{14}-$, $-NR^{14}-CH_2-O-$, $-NR^{15}-CH_2-NR^{14}-$, $-NR^{14}-CH_2-CH_2-O-$, $-O-CH_2-CH_2-NR^{14}-$, $-NR^{15}-CH_2-CH_2-NR^{14}-$, - wherein R^{14} and R^{15} each, independently from each other, are selected from the group of hydrogen, alkyl, Ar, Ar-alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkylcarbonyl and mono- or di(alkyl)aminocarbonyl ;

a and b are asymmetric centres ;

$(CH_2)_m$ is a straight hydrocarbon chain of m carbon atoms, m being an integer ranging from 1 to 4 ;

Pir is a radical according to any one of Formula (IIa), (IIb) or (IIc)



(a) (b) (c)

optionally substituted with n radicals R^8, wherein :

each R^8 is independently from each other, selected from the group of hydroxy, amino, nitro, cyano, halo and alkyl ;

n is an integer ranging from 0 to 5 ;

R^9 is selected from the group of hydrogen, alkyl and formyl ;

R^3 represents an optionally substituted aromatic homocyclic or heterocyclic ring system together with an optionally substituted and partially or completely hydrogenated hydrocarbon chain of 1 to 6 atoms long with which said ring system is attached to the Pir radical and of which may contain one or more heteroatoms selected from the group of O, N and S ;

alkyl represents a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, optionally substituted with one or more methyl, halo, cyano, oxo, hydroxy, alkyloxy or amino radicals ;

alkenyl represents a straight or branched unsatured hydrocarbon radical having one or more double bonds, optionally substituted with one or more methyl, halo, cyano, oxo, hydroxy, alkyloxy or amino radicals ;

Ar represents phenyl or naphthyl, optionally substituted with one or more radicals selected from the group of alkyl, halo, cyano, oxo, hydroxy, alkyloxy and amino ; and

Het is a monocyclic heterocyclic radical selected from the group of azetidinyl, pyrrolidinyl, dioxolyl, imidazolidinyl, pyrrazolidinyl, piperidinyl, homopiperidinyl, dioxyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, imidazolidinyl, tetrahydrofuranyl, 2H-pyrrolyl, pyrrolinyl, imidazolinyl, pyrrazolinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl ; each radical optionally substituted with one or more radicals selected from the group of alkyl, Ar, Ar-alkyl, halo, cyano, oxo, hydroxy, alkyloxy and amino.

2. A compound according to claim 1, characterized in that

X is O ;

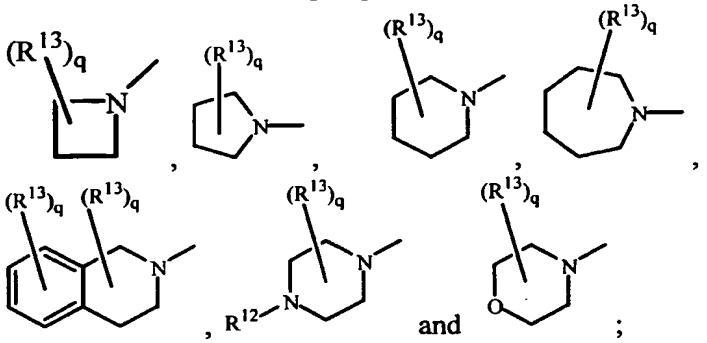
R^1 and R^2 are each selected from the group of hydrogen, N-$R^{10}R^{11}$ and alkyloxy ;

with the proviso that at least one of R^1 and R^2 is N-$R^{10}R^{11}$ wherein :

R^{10} and R^{11} are each, independently from each other, selected from the group of hydrogen, alkyl, Het, Ar, Ar-alkyl, Het- alkyl, mono- or di(alkyl)aminoalkyl, mono- or di(alkenyl)aminoalkyl, alkylcarbonyl, alkenylcarbonyl, Ar-carbonyl, Het-carbonyl, alkyloxycarbonyl, aminocarbonyl, mono- or di(alkyl)aminocarbonyl, mono- or di(Ar)aminocarbonyl, mono- or di(alkyloxycarbonylalkyl)aminocarbonyl, alkylcarbonyloxyalkyl, alkenylcarbonyloxyalkyl, mono-or di(alkyl)aminocarbonyloxyalkyl, N-benzylpiperazinyliminomethyl,

alkylsulphonyl and Ar-sulphonyl ; or

R^{10} and R^{11} may be taken together and with the N may form a monovalent radical selected from the group of



wherein :

R^{12} is selected from the group of hydrogen, alkyl, Ar, Ar-alkyl and Ar-alkenyl ;

each ring having optionally a double bond and each ring being optionally substituted with q radicals R^{13}, each radical R^{13} independently from each other selected from the group of alkyl, oxo and alkyloxycarbonyl and q being an integer ranging from 0 to 2 ; or

R^1 and R^2 may be taken together to form a bivalent radical $-O-CH_2-CH_2-NR^{14}-$ wherein R^{14} is selected from the group of hydrogen, alkyl, alkylcarbonyl, alkyloxyalkylcarbonyl and mono- or di(alkyl)aminocarbonyl ;

a and b are asymmetric centres ;

$(CH_2)_m$ is a straight hydrocarbon chain of m carbon atoms, m being an integer equal to 1 ;

Pir is a radical according to Formula (IIa)

R^3 represents an optionally substituted aromatic homocyclic or heterocyclic ring system together with an optionally substituted and partially or completely hydrogenated hydrocarbon chain of 1 to 6 atoms long with which said ring system is attached to the Pir radical and of which may contain one or more heteroatoms selected from the group of O, N and S ;

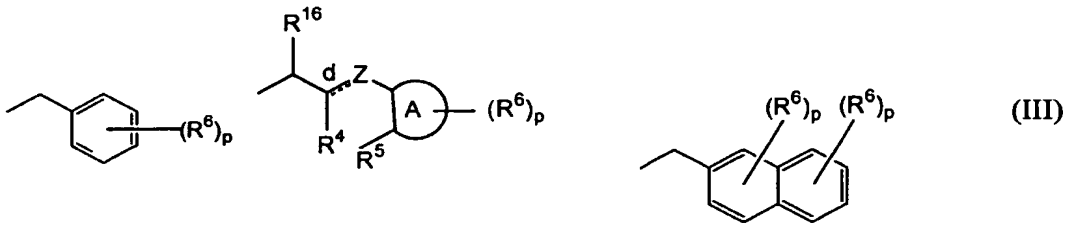
alkyl represents a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, optionally substituted with one or more methyl or amino radicals ;

alkenyl represents a straight or branched unsatured hydrocarbon radical having one or more double bonds, optionally substituted with one or more methyl radicals ;

Ar represents phenyl, optionally substituted with one or more radicals selected from the group of alkyl, halo, cyano, hydroxy and alkyloxy ; and

Het is a monocyclic heterocyclic radical selected from the group of azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, piperazinyl, N-benzylpiperazinyl, tetrahydrofuranyl and pyridinyl.

3. A compound according to any of claims 1 and 2, characterized in that R^3 is a radical according to any one of Formula (IIIa), (IIIb) or (IIIc)



(III)

(a) (b) (c)

wherein :

d is a single bond while Z is either a bivalent radical selected from the group of $-CH_2-$, -C(=O)-, -CH(OH)-, -C(=N-OH)-, –CH(alkyl)-, -O-, -S-, -S(=O)-, -NH- and –SH-; or Z is a trivalent CH-moiety that forms a covalent bond with R^4 equal to alkyl, such that a cycloalkyl moiety is formed ; or d is a double bond while Z is either a trivalent radical of formula =CH- or =C(alkyl)- ; or Z is a trivalent CH-moiety that forms a covalent bond with R^4 equal to alkyl, such that a cycloalkenyl moiety is formed ;

A is a 5- or 6-membered aromatic homocyclic or heterocyclic ring, selected from the group of phenyl, pyranyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, oxadiazolyl and isoxazolyl ;

p is an integer ranging from 0 to 6 ;

R^4 and R^5 are each, independently from each other, selected from the group of hydrogen, alkyl, Ar, biphenyl, halo and cyano ; or

R^4 and R^5 may be taken together to form a bivalent radical $-R^4-R^5-$ selected from

the group of $-CH_2-$, =CH-, $-CH_2-CH_2-$, -CH=CH- , -O-, -NH-, =N-, -S-, $-CH_2N(-alkyl)-$, $-N(-alkyl)CH_2-$, $-CH_2NH-$, $-NHCH_2-$, -CH=N-, -N=CH-, $-CH_2O-$ and $-OCH_2-$;

each R^6 is independently from each other, selected from the group of hydroxy, amino, nitro, cyano, halo, carboxyl, alkyl, Ar, alkyloxy, Ar-oxy, alkylcarbonyloxy, alkyloxycarbonyl, alkylthio, mono- and di(alkyl)amino, alkylcarbonylamino, mono- and di(alkyl)aminocarbonyl, mono- and di(alkyl)aminocarbonyloxy, mono- and di(alkyl)aminoalkyloxy ; or

two vicinal radicals R^6 may be taken together to form a bivalent radical $-R^6-R^6-$ selected from the group of $-CH_2-CH_2-O-$, $-O-CH_2-CH_2-$, $-O-CH_2-C(=O)-$, $-C(=O)-CH_2-O-$, $-O-CH_2-O-$, $-CH_2-O-CH_2-$, $-O-CH_2-CH_2-O-$, -CH=CH-CH=CH-, -CH=CH-CH=N-, -CH=CH-N=CH-, -CH=N-CH=CH-, -N=CH-CH=CH-, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-C(=O)-$, $-C(=O)-CH_2-CH_2-$, $-CH_2-C(=O)-CH_2-$ and $-CH_2-CH_2-CH_2-CH_2-$; and

R^{16} is selected from the group of hydrogen, alkyl, Ar and Ar-alkyl.

4. A compound according to any of claims 1 to 3, characterized in that R^3 is a radical according to any one of Formula (IIIa), (IIIb) or (IIIc) wherein :

d is a double bond while Z is a trivalent radical of formula =CH- or =C(alkyl)- ;

A is phenyl,

p is an integer equal to 0 or 1 ;

R^4 and R^5 are each, independently from each other, selected from the group of hydrogen and alkyl ;

each R^6 is halo ; and

R^{16} is hydrogen.

5. A compound according to any of claims 1 to 4, characterized in that X=O, one of R^1 and R^2 is hydrogen, methoxy or ethoxy ; m = 1 ; Pir is a radical according to Formula (IIa) wherein n =0 ; R^3 is a radical according to Formula (IIIb) wherein Z is =CH-, d is a double bond, A is a phenyl ring, R^4 is methyl and R^5 and R^{16} are each hydrogen.

6. A compound according to any of claims 1 to 5, characterized in that R^1 is hydrogen or methoxy and R^2 is an amine radical $NR^{10}R^{11}$; X=O ; m = 1 ; Pir is a radical according to Formula (IIa) wherein n = 0 ; R^3 is a radical according to Formula (IIIb) wherein Z is =CH-, d is a double bond, A is a phenyl ring, R^4 is methyl and R^5

and R^{16} are each hydrogen.

7. A compound according to any one of claims 1-6 for use as a medicine.

8. A compound which is degraded *in vivo* to yield a compound according to any one of claims 1-6.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient a therapeutically effective amount of a compound according to any one of claims 1-6 or a compound according to claim 7.

10. A process for making a pharmaceutical composition according to claim 9, comprising mixing a compound according to any one of claims 1-6 or a compound according to claim 8 and a pharmaceutically acceptable carrier.

11. The use of a compound according to any one of claims 1-6 or a compound according to claim 8 for the manufacture of a medicament for treating depression, anxiety and body weight disorders.

12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient a therapeutically effective amount of a compound according to any one of claims 1-6 or a compound according to claim 7 and one or more other compounds selected from the group of antidepressants, anxiolytics and antipsychotics.

13. The use of a pharmaceutical composition according to claim 12 for the manufacture of a medicament to improve efficacy and/or onset of action in the treatment of depression, anxiety and body weight disorders.

14. The use of a compound according to any one of claims 1-6 or a compound according to claim 8 for the manufacture of a medicament for the treatment of depression, anxiety and body weight disorders, said treatment comprising the simultaneous or sequential administration of a compound according to any one of claims 1-6 or a compound according to claim 8 and one or more other compounds selected from the group of antidepressants, anxiolytics and antipsychotics.

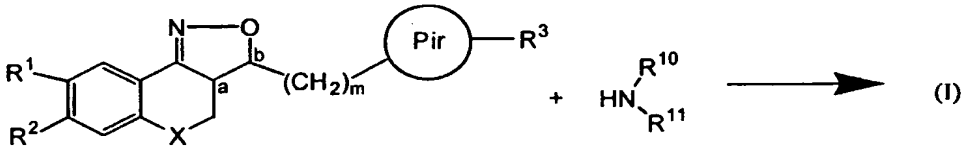
15. The use of one or more compounds selected from the group of antidepressants,

anxiolytics and antipsychotics for the manufacture of a medicament for the treatment of depression, anxiety and body weight disorders, said treatment comprising the simultaneous or sequential administration of one or more compounds selected from the group of antidepressants, anxiolytics and antipsychotics and a compound according to any one of claims 1-6 or a compound according to claim 8.

16. The use of a pharmaceutical composition according to claim 12 to improve efficacy and/or onset of action in the treatment of depression, anxiety and body weight disorders.

17. A process for making a pharmaceutical composition according to claim 12, comprising mixing a compound according to any one of claims 1-6 or a compound according to claim 8 and a compound selected from the group of antidepressants, anxiolytics and antipsychotics and a pharmaceutically acceptable carrier.

18. A process for preparing a compound according to Formula (I), characterized in that a compound according to Formula (IV) is reacted with an amine of Formula (V) according to the following reaction



(IV) (V)

wherein all variabeles, except for R^1 and R^2, have the same meaning as in Formula (I), at least one of R^1 and R^2 is an halogen and at most one of R^1 and R^2 is selected from the group of .hydrogen, hydroxy, cyano, halo, OSO_2H, OSO_2CH_3, N-$R^{10}R^{11}$, alkyloxy, alkyloxyalkyloxy, alkyloxyalkyloxyalkyloxy, tetrahydrofuranyloxy, alkylcarbonyloxy, alkylthio, alkyloxyalkylcarbonyloxy, pyridinylcarbonyloxy, alkylcarbonyloxyalkyloxy, alkyloxycarbonyloxy, alkenyloxy, alkenylcarbonyloxy and mono-or di(alkyl)aminoalkyloxy.